The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte EUGENI A. VAISBERG, CYNTHIA L. ADAMS, JAMES H. SARBY and ANNE M. CROMPTON

MAILED

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PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 2006-2341
Application No. 09/311,996

ON BRIEF

Before GRIMES, GREEN, and LEBOVITZ, Administrative Patent Judges.

LEBOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a computer program for determining the effects of a manipulation on cells. The examiner has rejected the claims as lacking written description and obvious over prior art. We reverse the written description rejection and affirm the rejection over prior art.

Background

The application describes computer software for characterizing the effects of drugs and other agents ("manipulations") on the structure and morphology of cells. Specification, page 2, lines 27-31; page 11. A computer program is

provided which can collect digital images of cells, and then extract features of the cells that appear in the images. The cells are exposed to manipulations, such as contact with drugs or other pharmaceutical agents, and the images before and after exposure are analyzed to characterize how the manipulation affects the cell. Id., page 3, lines 3-16. The information gathered from this process can be processed mathematically, e.g., using principal component analysis, to produce a "fingerprint" of the manipulation. Id., page 12, lines 15-28; page 24, lines 14-27. A fingerprint is a composite of two more features of the cells. Id. The fingerprint can be stored in a database and used to predict and understand the mechanism of perturbations on cells. Id., pages 24-25.

Discussion

Claim construction

Claims 49-57, 60, 61, and 63-66 are appealed. There are three grounds of rejection. Brief, page 13. Within each ground of rejection, the claims have been argued as a group, with no separate reasons for patentability of any of the claims. Consequently, the claims stand or fall together in each ground of rejection. We consider claim 49 as representative of the claims.

> 49. A computer program product for determining a property of a manipulation based upon determination of effects of said manipulation on a plurality of different cell types, said computer program product comprising:
>
> code for receiving one or more images of a plurality of components of a plurality of cells, wherein said plurality of cells are of different cell types and wherein said plurality of cells have been exposed to the manipulation;

code for determining a plurality of features of said plurality of components of said plurality of cells of different cell types;

code for analyzing said plurality of features to yield a plurality of descriptors, wherein some of said features are from a first cell type and some of said features are from a second cell type, and wherein some of said features from a first cell type are combined with features from a second cell type to yield one or more composite descriptors;

code for performing principal component analysis on said plurality of descriptors wherein at least one of said plurality of descriptors is a composite descriptor, whereby said descriptors are reduced to yield a fingerprint;

code for determining properties of said manipulation based upon said principal component analysis; and

a computer readable storage medium comprising said computer program product.

The claimed program has five basic functions: 1) receiving images of cell components from different cell types which have been subjected to a manipulation; 2) determining features of the cell components; 3) analyzing the features to yield descriptors, where some of the descriptors are "composite descriptors" that combine features from a first and second cell type; 4) performing principal component analysis on the descriptors to yield a fingerprint; and 5) determining properties of the manipulation based on the fingerprints obtained from the principal component analysis.

Examples of cell "components" are listed in the specification. Specification, page 8, lines 12-21; pages 9-11. These include: organelles, structures (e.g., membranes and cytoskeleton), and biomolecules (e.g., proteins, DNA, and lipids). The manipulations to which the cells can be exposed include "chemical, biological, mechanical" and five other broad classes of perturbations that a cell can

experience. Id., page 11. In the examples, cells are contacted with drugs having a known mechanism of action. Id., pages 31-32.

Features are described in the application as cell area, cell perimeter, intensity (e.g., when stained with a fluorescent marker), and other attributes which can be extracted from an image. Id., page 16, lines 15-18. A descriptor is determined from the features. Id., page 16, lines 18-21. It is described in the specification as a scalar or vector quantity. Id. An example is provided of a "shape" descriptor which is derived from area and perimeter features. Id.

Principal component analysis can be utilized to create "fingerprints" by mathematically combining the descriptors. Id., page 12, lines 26-27. The fingerprints can be used to understand the mechanism of drugs and other manipulations performed on cells, and to classify compounds with unknown mechanisms of action. Id., page 14, line 23-page 15. This information can also be used to predict behaviors, such as animal model effectiveness and patient responses. Id., page 24, lines 21-27.

Written description under § 112, first paragraph

Claims 49-57, 60, 61, and 63-66 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. According to the examiner, the specification does not describe "composite descriptors or descriptors which comprise different features of different cell types." Answer, page 3. The rejection apparently stems from an amendment filed April 6, 2004, in which claim 49 was amended by adding the phrase: "wherein at least one of said plurality

of descriptors is a composite descriptor resulting from the combination of features from cells of different cell types." Amendment filed April 6, 2004, page 2.

There is no requirement that the claimed invention be described in the identical wording that was used in the specification, as long as there is sufficient disclosure to show one of skill in this art that the inventor "invented what is claimed." Union Oil Co. of California v. Atlantic Richfield Co., 208 F.3d 989, 1000, 54 USPQ2d 1227, 1235 (Fed. Cir. 2000); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

After reviewing the specification, especially the passages cited by Appellants in their Brief, we are persuaded that the claimed subject matter is adequately described in the patent application, albeit not in identical wording. For instance, on page 3, lines 7-8, it is stated that descriptors can be formed from "two or more cell components." We see no reason to restrict this disclosure to components of the same cell or cell type, when the specification discloses performing measurements on multiple cell lines. Specification, page 28, lines 1-3; page 32, line 32-page 33, line 2. This rejection is therefore reversed.

Obviousness under 35 U.S.C. § 103

Claims 49-57, 60, 61, and 63-65 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Pauwels[1] in view of Paull.[2]

[1] Pauwels et al. (Pauwels), Journal of Pharmacological and Toxicological Methods, 37,105-115, 1997.
[2] Paull et al. (Paull), Journal of the National Cancer Institute, 81(14):1088-1092, 1989.

Pauwels describes the computer-assisted microscope image analysis of cells which have been treated with antineoplastic drugs. Pauwels, page 105, Abstract. Feulgen-stained nuclei were monitored by digital analysis to quantify the morphological effects induced by antineoplastic drugs. Id. Nuclei images were captured digitally and then characterized by 15 different parameters. Id., page 107, "Image Analysis." The parameters were combined and described by means of principal component analysis which "allows projection into a 2-dimensional space" of the 15 parameters. Id., page 109, column 2.

Paull studied the growth inhibiting effects of drugs on cell lines. Paull, page 1088. A computer program was developed that would derive, using an algorithm, the "mean graph" for cells exposed to the same drug. Id., page 1089, columns 2-3, "Mean Graph." This algorithm used the mean IC_{50} for all cell lines exposed to the same drug to calculate differential growth inhibition of a single cell line. Id.

The examiner rejected the claims over the combination of Pauwels and Paull, providing the following reasoning:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to write a computer program to perform the method of Pauwels et al. because Pauwels et al. shows use of algorithms to analyze cell image data and Paull et al. shows a computer program that performs similar analysis of drug treated tumor cell lines. It would have been further obvious to modify the method of Pauwels et al. by construction of descriptors or fingerprints derived from the plurality of tumor cell lines tested by Pauwels et al. because Paull et al. shows that consideration of data from a plurality of tumor cell lines allows for drugs to be clustered by mode of action or structure while considering their effects on a wide range of tumor cell types.

Answer, page 5.

Appellants challenged the rejection, arguing that there was no motivation to combine the references, and that even if combined, the skilled worker would have had no reasonable expectation of success in using Paull's single variant approach (i.e., differential growth inhibition) in Pauwels' method which required information on 15 parameters to enable the pharmacological classes of the drugs to be distinguished one from another. Brief, page 21.

In order to establish a case of prima facie obviousness, it must be shown that all elements of a claimed invention are found in a combination of prior art references and that the person of ordinary skill in the art would have been motivated with a reasonable expectation of success to have made the claimed composition or device, or carry out the claimed process. Velander v. Garner, 348 F.3d 1359, 1363, 68 USPQ2d 1769, 1772 (Fed. Cir. 2003).

First, we address the sufficiency of the prior art in meeting the requirement that all elements of claim 49 are disclosed in the combination of Pauwels and Paull. Our findings are summarized as follows:

• "code for receiving one or more images of a plurality of components of a plurality of cells, wherein said plurality of cells are of different cell types," and where the cells have been exposed to a "manipulation."

Three different cell lines ("cells of different types") were utilized in Pauwels: MXT, J82, and T24. Pauwels, page 106, column 2 ("Cell Culture"). The cells were exposed to different antineoplastic drugs ("the manipulation") and then stained with Feulgen reagent, a nuclear stain. Id., page 106, Table 1; page 107, column 1 ("Preparation of the Samples to be Analyzed."). Images of the Feulgen-stained

nuclei ("components") were collected from microscope slides and stored as digitized images ("code for receiving one or more images of a plurality of components"). Id., page 107.

• "code for determining a plurality of features of said plurality of components"

Image analysis of the nuclei ("components") involved measurement of features that included, optical density and chromatin texture. Id., page 107, column 2.

• "code for analyzing said plurality of features to yield a plurality of descriptors"

The features extracted from the digital images were used to compute 15 different parameters ("descriptors"). Id., page 107, column 2 ("Image Analysis"). These included mean optical density, variance of optical density, skewness, and kurtosis. Id.

• "code for performing principal component analysis ... to yield a fingerprint"

Multivariate analysis was performed by principal-component analysis. Id., page 109, column 2 ("Multivariate analysis"). "This mathematical analysis of data allows a projection into a 2-dimensional space of the 15-dimensional space corresponding to the multiparametric image featuring the 15 parameters computed on each nucleus." Id. The multiparametric image ("fingerprint") was utilized to determine properties of the drugs. See, e.g., id., Figs. 3-6.

• "code for determining properties of said manipulation based upon said principal component analysis"

The results of the principal component analysis were graphed and analyzed to determine the effects of the drug-induced morphological changes on cells. The results showed "that it is possible to identify distinct classes of antineoplastic drugs on the basis of their mechanisms of action by means of the quantitative chromatin pattern description of Feulgen-stained nuclei." Id, page 105, Abstract; pages 110-111.

In sum, as detailed above, we find that examiner correctly concluded that all elements of the claimed subject matter can be found in Pauwels, with the exception of the "composite descriptor." Answer, page 5, lines 2-3. To make up for Pauwels' deficiency, the examiner cited Paull. According to the examiner, it would have been obvious to have employed Paull's teaching in Pauwels because Paull shows that data (descriptors) from a plurality of cells is useful for clustering drugs based on their mechanism of action. Answer, page 5.

We find the examiner's reasoning to be persuasive. Paull's concern was the problem in detecting differences in growth inhibition (a single variable) between the 50 cell line panel (a plurality of cell lines). To address it, Paull developed a "mean graph" that relied on a composite feature of all cell lines ("mean of the logarithmic value of the IC_{50} values for all cell responses measured for a compound") as an anchor point to compare the IC_{50} of each individual cell line. Paull, page 1089, paragraph spanning columns 2-3. This was implemented in a computer program named "COMPARE." Paull did not view their mean graph analysis to be restricted to the problem addressed in their publication.

> These procedures are conceptually centered in the mean graph, which was designed to graphically represent screening results for individual compounds tested against large numbers of tumor cell lines. Experimental applications of the COMPARE program to a limited data base accrued from the pilot screen suggest the possibility of meaningful clustering of mean graph patterns that is related to biological properties and/or chemical structure and properties.

Id., page 1092, column 2.

In our view, the examiner correctly concluded that the skilled worker would have recognized the advantage of Paull's computer program for analyzing drug effects on cells, and would have been motivated to have applied it to the image analysis performed by Pauwels. Answer, page 5; page 10, lines 1-4.

It does not concern us that there is no express suggestion in the prior art to modify Pauwels with Paull's method. A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art. "[T]he teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kahn, 441 F.3d 977, 987-988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

Like the Pauwels publication, Paull characterizes the activity of anticancer drugs with the purpose to develop methods to identify new anticancer drugs. Paull, page 1089, column 1, paragraphs 1-2. Differential growth inhibition was "systematically investigated as a criterion for new drug selection." Id. A panel of 50 cell lines was used. Id., page 1089, paragraph 3. This is the same field of

endeavor described in the Pauwels publication where the authors similarly stated their goal to establish "data banks" that could be used to characterize the activity of new drugs. See e.g., Pauwels, pages 105-106.

Both prior art references are focused on determining "properties" of drugs ("manipulations) – the step required by claim 49 – to classify and predict their mechanism of the action. In this context, Paull discloses a computer program that is an algorithm to calculate a fingerprint ("mean graph") of differential growth activity from descriptors (IC_{50}) of 50 different cell types. The success of this technique would have reasonably suggested its applicability to other descriptors, including the descriptors used in the image analysis taught by Pauwels, because the nature of the problem addressed by the references is the same. Kahn, 441 F.3d at 987-988, 78 USPQ2d at 1336.

Appellants argued that rejection is improper because the single-variant approach utilized by Paull was rejected by Pauwels who found it "necessary to combine the information on the 15 parameters into one calculation step." Brief, page 20. Based on data in Pauwels, they say "Pauwels sensibly cautioned persons skilled in the art to avoid the single-parameter method taught by Paull, if the goal is to distinguish cell-drug interaction." Id (emphasis removed).

The examiner's rejection did not abandon Pauwels' multivariate approach. Rather, his position is that it would have been obvious to the skilled worker to have utilized the composite descriptor taught by Paull in Pauwels' multivariate analysis. Answer, page 5. As pointed out by the examiner, Pauwels' approach is not

inconsistent with Paull. Id., page 10, lines 1-4. Appellants did not identify why Pauwels' method would be defeated by the addition of a composite descriptor.

Along these same lines, Appellants also argued:

> ... even if the teachings of Pauwels and Paull were combined, the person of ordinary skill in the art would have no reasonable expectation of success in using Paull's single variant approach when Pauwels teaches that it is "necessary to combine the information on the 15 parameters into one calculation step" in order to "enable the pharmacological classes of the drugs to be distinguished one from another."

Brief, page 21.

Appellants have not made it clear why incorporating a parameter derived from multiple cell lines would unravel the expectation that Pauwels' principal component analysis would succeed.

In sum, Appellants have not convinced us that the examiner's rejection was improper. Accordingly, we conclude that the examiner has provided sufficient evidence to establish a case of prima facie obviousness. This rejection is affirmed. Claims 49-57, 60, 61, and 63-65 fall together since Appellants did not provide arguments separately addressing their patentability.

Rojanaskul

Claims 63 and 66 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Pauwels in view of Paull as applied to claims 49-57, 60, 61, and 63-65, and further in view of Rojanaskul.

Claim 66 requires the selection of the manipulation of claim 49 from a list of ten. Among the list is "applying an antisense oligonucleotide," the species which is subject of the instant rejection. As indicated in Appellants' Brief, claim 63 was

improperly grouped with claim 66 since it does not refer to antisense oligonucleotides. Although the examiner in responding to the Brief failed to acknowledge this error, we find it harmless since claim 63 had already been rejected over the combination of Pauwels and Paull.

Rojanasakul is a review of antisense oligonucleotides and their use "for the treatment of human diseases such as virus associated illnesses and cancers." Rojanasakul, page 115, Abstract. According to the examiner, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have treated the cells with antisense oligonucleotides "because Rojanasakul shows that antisense oligonucleotides have potential as therapeutic drugs and manipulation of cells with antisense oligonucleotides allows for study of their effects on cell lines and for comparison with the effects of other drugs." Answer, page 6.

As we understand it, the examiner's position is that the Pauwels and Paull publications would have reasonably motivated a person of skill in the art to replace the anticancer drugs disclosed in those publications with oligonucleotides. We agree.

Pauwels discloses a list of 30 antineoplastic drugs belonging to different pharmacological classes. Pauwels, Abstract. In the introduction, the authors described their aim to be the construction of a database of morphonuclear-induced effects of antineoplastic drugs that could be used to characterize the mechanism of action of new investigational drugs. Id., page 105, column 2. Similarly, Paull stated that their methods were useful in determining the activity of drugs in the

National Cancer Institute's drug screening efforts. Paull, page 1089. They described the use of 88 different compounds. Id., page 1092, Table 2. In both publications, the methods are described as being useful to screen the activity of any drug. There is no preference in either publication for a particular drug class or structure. To the contrary, the authors encourage screening new drugs for activity. Thus, we share the examiner's view that, in the context of the methods disclosed in Pauwels and Paull, the drugs are interchangeable and have no distinguishing feature other than being candidates for the disclosed analytical methods. Appellants did not specifically identify any defect in the examiner's reasoning. Brief, page 24.

Having provided adequate evidence of prima facie obviousness, we affirm the examiner's rejection.

Summary

The rejection of claims as lacking written description is reversed. The rejection of claims as obvious over prior art is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Eric B. Grimes)
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